PATENT
Application No. 09/868,379
Filing Date: 08/15/2001
Examiner: Lezah Roberts
Art Unit: 1612
Attorney Docket No. 2006-219/H03763

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the United States Patent Application of :
Applicants: Christian Kropf,
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Continuation of International Application
PCT/EP99/09683, filed 12/09/1999
Claiming German priority of
Application No. 198 53 662.0, filed 12/18/1998

Examiner: Frederick F. Krass
Art Unit: 1614

Title: **FINE SUSPENSIONS OF POORLY SOLUBLE CALCIUM SALTS AND THEIR USE IN DENTAL CARE PRODUCTS**

FOURTH DECLARATION OF CHRISTIAN KROPF

I, Christian Kropf declare as follows:

1. I am an inventor of United States Patent Application No. 09/868,379.

2. I am the head of a group in Laundry and Homecare Global Research Chemistry at Henkel AG & Co. KGaA, Henkelstrasse 67, 40589 Düsseldorf, Germany. I obtained both a diploma degree in Chemistry in 1992 and a Ph.D. degree in Engineering Sciences (new materials) in 1998 from Saarland University in Saarbruecken, Germany.

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3. I am familiar with United States Patent Application No. 09/868,379 of Christian Kropf et al. (hereinafter the "Kropf application") and United States Patent No. 5,560,932 to Bagchi et al.

4. Claim 8 of the Kropf application is directed to a suspension. The remaining claims 9, 13-16 and 20-25 are directed to a toothpaste comprising the suspension, or other suspensions within the scope of claim 8. Claim 8 reads as follows:

> Claim 8. A suspension of one or more phosphate calcium salts, fluoride calcium salts, or fluorophosphate calcium salts in a liquid medium in which the salts are less than 1 g/l soluble, wherein the calcium salts comprise primary particles having diameters of from 5 to 50 nanometers and lengths of from 10 to 150 nanometers, wherein the calcium salts are formed by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate or fluoride salts at an increased pH using an aqueous alkali or ammonia and in the presence of a content of at least 0.01% by weight, based on the weight of the suspension, of a water-soluble polymeric protective colloid selected from the group consisting of gelatin, casein, starch, plant gums, cellulose ethers, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxyethylstarch and hydroxypropylguar, resulting in the colloid being adsorbed onto said particles and the particles being stabilized against agglomeration.

5. The Bagchi et al. patent describes the preparation of a nanoparticulate dispersion and the resulting nanoparticles. The process is summarized in the Abstract, the pertinent portion of which is set forth below.

> This invention describes the preparation of nanoparticulate pharmaceutical agent dispersion via a process that comprises the dissolution of the said pharmaceutical agent in an alkaline solution and then neutralizing the said solution with an acid in the presence of a suitable surface-modifying, surface-active agent to form a fine particle dispersion of the said pharmaceutical agent.

6. Bagchi et al. discloses the objective of its invention at column 3, lines 7-16, which is quoted herebelow:

> It would be desirable to provide stable dispersible drug or pharmaceutical agent particles in submicron size range which can be readily prepared which do not appreciably flocculate or agglomerate due to interparticle attraction forces, and do not require the presence of a crosslinked matrix, simultaneously providing enhanced bioavailability of the drug. Furthermore, it would be highly desirable that such formulations do not involve removal of toxic residues such as toxic solvents or heavy metal solubilizates that arise out of attrition of the milling media.

7. The accomplishment of this objective by the Bagchi et al. invention is relevant to the following description of the advantages of the invention.

> It is an advantageous feature that a wide variety of surface modified drug nanoparticles free of unacceptable contamination can be prepared in accordance with this invention. (Column 3, lines 50-52).
>
> A further advantage of the method is that unlike solvent precipitation, the final product of this invention is free of any trace of trace solvents that may be toxic and must be removed by expensive treatments prior to final product formulation. (Column 4, lines 7-11).

8. The particles of the invention, the process of making the particles and a preferred utility are disclosed in the paragraph directly under the heading "Description of Preferred Embodiments." That paragraph is set forth below.

> This invention is based partly on the discovery that pharmaceutical agent particles having an extremely small effective average particle size can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier, and that such particles are stable and do not appreciably flocculate or aggregate due to interparticle attractive force and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. (Column 4, lines 40-48).

9. Bagchi et al. discloses that the particles comprise a pharmaceutical agent substance in a discrete crystalline phase. (Column 4, lines 56–61).

10. Bagchi et al. discloses that the surface modifier physically adheres to the surface of the particles but is free of intermolecular linkages between the molecules of the modifier, and between the modifier and the particles, due to the lack of chemical bonds between the surface modifier and [drug] particle. This disclosure in Bagchi et al. is set forth at column 5, lines 40–43 and in the passage herebelow:

> The surface modifier is adsorbed on the surface of the pharmaceutical agent in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages. (Column 6, lines 20–26).

11. Applicants' process of making the particles is different from the process used to make the Bagchi et al. particles. Applicants' process as disclosed in the Specification at page 7, lines 13–19, prepares the claimed suspensions by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate or fluoride salts in the presence of water-soluble polymeric protective colloids. Applicants' precipitation reactions are carried out at an increased pH using an aqueous alkali or ammonia. The Bagchi et al. process begins with the dissolution of a pharmaceutical agent in an aqueous base and the addition of an aqueous surfactant solution followed by the addition of an acid solution to form a nanoparticulate dispersion. (*See* Steps 1–3 on the cover sheet of the Bagchi et al. patent). As noted above in Paragraph 8, the Bagchi et al. particles can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier.

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12. Unlike the Bagchi et al. process in which the particles are formed by homogeneous nucleation, the calcium salt particles of Applicants' claimed suspension are formed from precipitation reactions of acidic aqueous solutions of water-soluble calcium salts and of aqueous solutions of water-soluble phosphate or fluoride salts. Applicants' precipitation reactions occur under conditions of increasing pH using an aqueous alkali or ammonia in the presence of one or more of Applicants' claimed colloids rather than under conditions of decreasing pH as disclosed in Bagchi et al. Applicants' precipitation reactions of acidic aqueous solutions of water-soluble calcium and phosphate or fluoride salts, in the presence of the colloid, and at an increasing pH, results in particles having a more intense structure in which, in Applicants' claimed particles, the colloid forms intermolecular crosslinkages. In contrast, in the Bagchi et al. particles, the surface modifiers [*i.e.*, colloid] are essentially free of intermolecular crosslinkages.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States Code, and that such willful false statements may jeopardize the validity of the Kropf application or any patent issued thereon.

Dated: September 30, 2008

CHRISTIAN KROPF